REMARKS

In the Office Action, the Examiner reopened the prosecution of the application. In response, Applicant elects to file this reply under 37 C.F.R. § 1.111.

The Examiner has rejected Claims 7-11 and 15-19 as obvious under 35 U.S.C. § 103(a) in view of one or more prior art references.

By this amendment, Claim 7 has been amended to more clearly define the present invention. The support for amended Claim 7 may be found at page 8, lines 16-22 of the specification. No new matter has been added thereby. Accordingly, Claims 7-11 and 15-19 are currently pending in the application. The Examiner's rejections are traversed below.

Claim Rejections - 35 U.S.C. § 103 (Vacanti)

The Examiner has rejected Claims 7-9, 11, 15, and 19 under 35 U.S.C. § 103(a) as being unpatentable over Vacanti, et al., U.S. Patent No. 5,855,610.

As amended, Claim 7 limits the claimed reinforcement to one that is "integrated with the sponge and located inside or on the exterior surface of the matrix." Vacanti neither discloses nor suggests such a reinforcement.

As noted by the Examiner, see Office Action at 4, the only disclosure in Vacanti that corresponds to the claimed reinforcements are the "struts," which appear to be discussed only at col. 3, lns. 62-67 and col. 5, lns. 34-48. The struts are described as imparting "resistance to mechanical forces", thereby "yielding the desired shape." Vacanti '610 at col. 3, lns. 65-66. The exemplary applications of such struts are "heart valve 'leaflets' and tubes." *Id.* at col. 3, lns. 66-67. The single paragraph in which the struts are disclosed in detail is reproduced below:

> In some embodiments it may be desirable to create additional structure using devices provided for support, referred to herein as "struts." These can be biodegradable or non-degradable polymers which are inserted to form a more defined shape than is obtained using the cell-matrices. An analogy can be made to a corset, with the struts acting as "stays" to push the surrounding tissue and skin up and away from the implanted cells. In a preferred embodiment, the struts are implanted prior to or at the time of implantation of the cell-matrix structure. The struts are formed of a polymeric material of the same type as can be used to form the matrix, as listed above, having sufficient strength to resist the necessary mechanical forces.

The structural relationship between the struts and the cell-matrix structure is not specifically disclosed in this paragraph. Nevertheless, the struts are said to function in the manner of corset stays, exerting force on the tissue and skin surrounding an implanted graft to push it "up and

away from the implanted cells" (emphasis added). The struts also may be implanted prior to the implantation of the cell-matrix structure. These disclosures strongly suggest that rather than being "integrated with the sponge", as required by amended Claim 7, the struts are entirely separate from the cell-matrix structure. Thus, the only suggestion in this reference is to use a matrix unlike that presently claimed.

Moreover, there is also no disclosure or suggestion in the cited prior art reference that the struts should be located inside the matrix or on the exterior surface thereof, as required by amended Claim 7. If the struts were located within the cell-matrix structure, for example, they would be unable to perform the disclosed function of "push[ing] the surrounding tissue and skin up and away from the implanted cells." Rather, at least some of the cells would be forced against the surrounding tissue by action of the internal struts. Similarly, struts that were integral with and on the exterior surface of the cell-matrix structure would leave the implanted cells at the surface of the matrix in contact with the surrounding tissue or skin, which is inconsistent with the disclosed function of pushing the tissue or skin "away from" the matrix.

With respect to the examples cited by the Examiner at pages 4-5 of the Office Action, Applicant notes that neither example discloses the use of the "struts" that the Examiner equates with the claimed reinforcements. In Example 2, cardiovascular tissue (a blood vessel, as in pending Claim 8) was engineered, and the extracellular matrices of the resulting tissue were examined to determine if the engineered tissue had "the physical characteristics of native vascular tissues." Vacanti '610 at col. 9, lns. 7-11. The results showed that vascular tissue had been "successfully formed" without the use of reinforcements. *Id.* at lns. 13-14. Moreover, the engineered heart valve (as in pending Claim 9) of Example 1 was actually implanted into a sheep "to determine if the constructs had the required pliability and mechanical strength for use in patient." Vacanti '610 at col. 8, lns. 21-23. The results of the implantation are not given in the Vacanti reference. From this inclusion of this working example in the patent specification, however, one of skill in the art would assume that the unreinforced engineered heart valve performed adequately. In other words, Vacanti '610 discloses the engineering of unreinforced cardiovascular tissues that were found to have the physical characteristics of native tissue, and were actually tested in vivo and found to have the "required pliability and mechanical strength" for use in human beings. This testing would indicate to one of skill in the art that engineered cardiovascular tissue needed no reinforcement at all, let alone the specific claimed reinforcement

that is integral with the sponge of the matrix and inside or on the exterior surface thereof, as required by amended Claim 7. Vacanti '610 thus indicates (as does Naughton '531, as discussed below) that the replacement tissues grown on the disclosed unreinforced matrix have sufficient strength to be implanted in the body as prosthetic cardiovascular tissue once the tissue culture is complete. One of skill in the art would simply not be motivated to modify the cell matrices of Vacanti '610 in the manner set forth in amended Claim 7. As such, the Vacanti '610 reference fails to support a *prima facie* showing of obviousness.

Furthermore, even had a *prima facie showing* of obusness been set forth, the presently claimed invention provides unexpected advantages that would effectively rebut such a showing. The integration of the claimed reinforcement with the sponge and locating it either inside or on the exterior surface of the matrix, as required by amended Claim 7, provides the unexpected advantages that a smooth sponge surface comes into contact with the blood flow, which is advantageous in that it reduces the likelihood that thromboses will be formed, enhances cell adhesion, promotes the smooth supply of nutrition to the cells, and enhances the formation of the tunica intima. These effects of the present invention could not have been expected from Vacanti '610 by a person skilled in the art. Accordingly, Vacanti '610 neither discloses nor suggests to one of skill in the art the use of a reinforcement which is integrated with the sponge and located inside or on the exterior surface of the matrix, as required by amended Claim 7. Accordingly, Vacanti '610 does not make obvious the invention of amended Claim 7.

Furthermore, Claims 8-11 and 15-19 depend from Claim 7, and thus incorporate all of the limitations thereof, as well as further limitations. For these reasons, Claims 7-9, 11, 15, and 19 are not obvious over Vacanti '610.

Claim Rejections - 35 U.S.C. § 103 (Vacanti/Fofonoff/Cox or Love)

The Examiner has rejected Claim 10 over the combination of Vacanti '610 with Fofonoff et al., U.S. Patent No. 5,882,929, taken with Cox, U.S. Patent No. 6,719,789, or Love, U.S. Patent No. 5,509,930. As described above, Vacanti '610 does not disclose or suggest a reinforcement that is integrated with the sponge and located inside or on the exterior surface of the matrix, as required by amended Claim 7. Fofonoff '929, Cox '789, and Love '930 do not disclose or suggest the use of reinforcements in the production of cardiovascular tissue, let alone the use of the specific claimed reinforcements. Accordingly, they cannot supply the disclosure

lacking in Vacanti '610. For that reason, Claim 10 is not obvious over this combination of references.

Claim Rejections - 35 U.S.C. § 103 (Vacanti/Vyakarnam/Morita)

The Examiner has rejected Claims 16-18 as obvious over Vacanti '610 and further in view of Vyakarnam, U.S. Patent No. 6,534,084, and Morita, Japanese Patent No. 3-23864. As described above, amended Claim 7 requires the use of a reinforcement made of a bioabsorbable material which is integrated with the sponge and located inside or on the exterior surface of the matrix. As described above, Vacanti '610 does not disclose or suggest these limitations. Neither do Vyakarnam '084 or Morita '864 disclose or suggest such a reinforcement for use in cardiovascular tissue.

As the Examiner indicates, Vyakarnam '084 discloses foam structures that can be composed of copolymers of lactide and which can be used to regenerate tissue, such as vascular grafts. Furthermore, as the Examiner notes, Vyakarnam teaches that the foam may be reinforced with fibers made of calcium phosphate. The discussion of fibers to which the Examiner refers is within a section of the Vyakarnam specification discussing cartilage. Here, however, the reinforcing fibers are restricted to a section of the cartilage that attaches to bone, in which sufficient stiffness is required:

> [A]t the bottom of this structure there is a need for larger pores (about 150 μm to about 300 μm) with higher stiffness to be structurally compatible with cancellous bone. The foam in this section could be reinforced with ceramic particles or fibers made up of calcium phosphates and the like.

Vyakarnam '084 at col. 6, lines 36-41 (emphasis added). Furthermore, Vyakarnam also discusses the use of fibers in tissue scaffoldings for bone repair, which would clearly also require significant stiffness. Vyakarnam '084 at col. 8, lines 5-12. But although Vyakarnam specifically describes possible tissue scaffoldings for use in vascular repair, the reference does not disclose the use of reinforcements in such applications. Vyakarnam accordingly suggests to one of skill in the art that the use of reinforcing fibers is only preferable where higher stiffness is required, such as in those parts of cartilage which are connected to bone or in bone itself, and that reinforcement should not be used for cardiovascular tissue. Much less does Vyakarnam suggest to one of skill in the art the use of the specific claimed reinforcement of amended Claim 7, which is integrated with the sponge and located inside or on the exterior surface of the matrix.

Furthermore, Morita '864 does not supply what is lacking in Vacanti '610 and Vyakarnam '084. An English-language translation of Morita '864 was previously submitted along with the amendment and response of September 19, 2005. Morita discloses a filler material for use in vivo that uses poly-L-lactic acid. Morita does not disclose seeding and growing cells on the filler material prior to implantation. Neither does Morita disclose that the filler material is used for regenerating blood vessels or similar cardiovascular tissue structures.

Morita clearly indicates that reinforcement is not necessary when fully regenerated tissue is present. Specifically, the implant disclosed in Morita is said to "maintain[] its strength and shape over a long period of time until the regeneration of the tissue." Morita translation at page 5, lines 13-14 (Morita '864 at page 7, lines 5-7). One of skill in the art would accordingly understand from Morita that if tissue was generated ex vivo by tissue engineering techniques, artificial reinforcement of the implant would not be necessary.

Moreover, Morita does not disclose or suggest that the reinforcement should be specifically located inside or on the exterior surface of the matrix, as required by the amended claims. Accordingly, the combination of references cited by the Examiner fail to support a *prima facie* showing of obviousness with respect to Claims 16-18, which are accordingly not obvious over this combination of references.

Claim Rejections - 35 U.S.C. § 103 (Naughton)

The Examiner has rejected Claims 7, 8, and 11 as obvious over Naughton et al., U.S. Patent No. 5,863,531. As amended, Claim 7 limits the claimed reinforcement to one that is "integrated with the sponge and located inside or on the exterior surface of the matrix." Naughton '531 neither discloses nor suggests such a reinforcement.

As the Examiner indicates, Naughton discloses foam structures that may be used in regenerating vasculature. However, Naughton does not teach the use of fibrous reinforcing materials, much less the specific reinforcement of amended Claim 7, which is integrated with the sponge and located inside or on the exterior surface of the matrix. Rather, Naughton indicates that tubular biological replacement tissues grown on an unreinforced matrix may be used as cardiovascular replacement tissues in vivo. The examples of tubular biological tissue engineering provided all use unreinforced mesh as the starting point. *See* Naughton '531 at col. 23. Furthermore, Naughton discloses that arterial structures grown in this way produce elastin, so as to "simulate . . . natural arterial walls." Naughton '531 at col. 25, lns. 10-11. Naughton

would accordingly suggest to one of skill in the art that the replacement tissues grown on unreinforced matrices or foams have sufficient strength to be implanted in the body as prosthetic cardiovascular tissue once the tissue culture is complete. Naughton thus does not disclose reinforcement of a matrix used to regenerate cardiovascular tissue.

Much less does Naughton disclose or suggest the specific reinforcement required by amended Claim 7, which is integrated with the sponge and located inside or on the exterior surface of the matrix. The Examiner states that "the extracellular matrix containing elastin produced during culturing to form the stromal tissue will result in a bioabsorbable material that provides reinforcement." Office Action at pages 11-12. However, elastin produced by pre-seeding the matrix with stromal cells as suggested by the Examiner will not constitute a reinforcement "integrated with the sponge," as required by amended Claim 7. Naughton '531 neither discloses nor suggests a reinforcement that is integrated with the sponge and located inside or on the exterior surface of the matrix. Therefore, Claim 7 is not obvious over Naughton '531.

Claims 8 and 11 depend from Claim 7, and thus incorporate all of the limitations thereof, as well as further limitations. For these reasons, Claims 8 and 11 are not obvious over Naughton '531.

Claim Rejections - 35 U.S.C. § 103 (Naughton/Vacanti)

The Examiner has rejected Claims 9, 15 and 19 as obvious over the combination of Naughton '531 and Vacanti '610. As amended, Claim 7 limits the claimed reinforcement to one that is "integrated with the sponge and located inside or on the exterior surface of the matrix." As described above, neither Naughton '531 nor Vacanti '610 discloses or suggests the use of a matrix comprising such a reinforcement. Accordingly, Claims 9, 15, and 19 are not obvious over the combination of Naughton '531 and Vacanti '610.

Claim Rejections - 35 U.S.C. § 103 (Naughton/Vacanti/Fofonoff/Cox or Love)

The Examiner has rejected Claim 10 as obvious over the combination of Naughton '531 and Vacanti '610, and in view of Fofonoff '929, Cox '789, and Love '930. As amended, Claim 7 limits the claimed reinforcement to one that is "integrated with the sponge and located inside or on the exterior surface of the matrix." As described above, none of Naughton '531, Vacanti '610, Fofonoff '929, Cox '789, or Love '930 discloses or suggests the use of a matrix comprising such a reinforcement. Accordingly, Claim 10 is not obvious over this combination of references.

Claim Rejections - 35 U.S.C. § 103 (Naughton/Vacanti/Vyakarnam/Morita)

The Examiner has rejected Claims 16-18 as obvious over the combination of Naughton '531, Vacanti '610, Vyakarnam '084, and Morita '864. As amended, Claim 7 limits the claimed reinforcement to one that is "integrated with the sponge and located inside or on the exterior surface of the matrix." As described above, none of Naughton '531, Vacanti '610, Vyakarnam '084, or Morita '864 disclose or suggest the use of a matrix comprising such a reinforcement. Accordingly, Claims 16-18 are not obvious over this combination of references.

Bell et al., 4,546,500

The Examiner has made Bell '500 of record "to further show reinforcement of engineered vessels." Office Action at 17. Applicant notes that Bell does not disclose a reinforcement made of a bioabsorbable material, as required by amended Claim 7. Rather, Bell incorporates a plastic mesh sleeve of Dacron, Teflon, or nylon. Bell '500 at col. 4, lns. 22-40.

CONCLUSION

In summary, integrating a reinforcement with the sponge and locating it either inside or on the exterior surface of the matrix, as required by amended Claim 7, provides sufficient strength to resist the pressure caused by blood flow in vivo, as shown by the in vivo animal study results disclosed on page 13 of the specification. In addition, the claimed invention provides the further unexpected advantages that a smooth sponge surface comes into contact with the blood flow, which is advantageous in that it reduces the likelihood that thromboses will be formed, enhances cell adhesion, promotes the smooth supply of nutrition to the cells, and enhances the formation of the tunica intima. These effects of the present invention could not have been expected from any of the prior art references, alone or in combination, by a person skilled in the art. Accordingly, the cited art neither discloses nor suggests to one of skill in the art the use of a reinforcement which is integrated with the sponge and located inside or on the exterior surface of the matrix, as required by amended Claim 7. Furthermore Claims 8-11 and 15-19 depend from Claim 7, and thus incorporate all of the limitations thereof, as well as further limitations. For these reasons, Claims 7-11 and 15-19 are not obvious over the cited art.

In view of the foregoing, the application is believed to be fully in condition for allowance, and allowance of the application is therefore respectfully requested. Should any remaining

impediments to allowance be identified by the Examiner, the Examiner is respectfully invited to contact the undersigned attorney at the telephone number appearing below.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. 11-1410.

Respectfully submitted,

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